

J Neurol (2012) 259:537–541
DOI 10.1007/s00415-011-6224-5

ORIGINAL COMMUNICATION

Predictive value of neurological examination for early cortical responses to somatosensory evoked potentials in patients with postanoxic coma

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Received: 2 July 2011 / Revised: 9 August 2011 / Accepted: 11 August 2011 / Published online: 2 September 2011
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Abstract Bilateral absence of cortical N20 responses of median nerve somatosensory evoked potentials (SEP) predicts poor neurological outcome in postanoxic coma after cardiopulmonary resuscitation (CPR). Although SEP is easy to perform and available in most hospitals, it is worthwhile to know how neurological signs are associated with SEP results. The aim of this study was to investigate whether specific clinical neurological signs are associated with either an absent or a present median nerve SEP in patients after CPR. Data from the previously published

multicenter prospective cohort study PROPAC (prognosis in postanoxic coma, 2000–2003) were used. Neurological examination, consisting of Glasgow Coma Score (GCS) and brain stem reflexes, and SEP were performed 24, 48, and 72 h after CPR. Positive predictive values for predicting absent and present SEP, as well as diagnostic accuracy were calculated. Data of 407 patients were included. Of the 781 SEPs performed, N20 s were present in 401, bilaterally absent in 299, and 81 SEPs were technically undeterminable. The highest positive predictive values (0.63–0.91) for an absent SEP were found for absent pupillary light responses. The highest positive predictive values (0.71–0.83) for a present SEP were found for motor scores of withdrawal to painful stimuli or better. Multivariate analyses showed a fair diagnostic accuracy (0.78) for neurological examination in predicting an absent or present SEP at 48 or 72 h after CPR. This study shows that neurological examination cannot reliably predict absent or present cortical N20 responses in median nerve SEPs in patients after CPR.

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Keywords Prognosis · Coma · Evoked potentials
somatosensory · Cardiopulmonary resuscitation ·
Neurologic examination

Introduction

Prediction of neurological outcome in comatose survivors of cardiopulmonary resuscitation (CPR) has been the subject of several studies in the last three decades [1–7]. In 2006, a practice parameter for the prediction of the outcome of postanoxic coma was published by the American Academy of Neurology [8]. Bilateral absence of cortical N20 responses of median nerve somatosensory evoked

potentials (SEP) 24 h after CPR, as well as absent pupillary light responses, absent corneal reflexes, and absent or extensor motor response to pain after 72 h, were all considered reliable predictors of a poor neurological outcome. In daily practice, a patient with postanoxic coma is examined by a neurologist before additional investigations are requested. Some clinical signs may be associated with the presence or absence of cortical N20 responses but to what extent is unknown. Knowledge of specific clinical signs that predict SEP results may optimize SEP requesting policy.

Methods

Data from the previously published multicenter prospective cohort study PROPAC (prognosis in postanoxic coma, 2000–2003) were used [5]. This study was performed before hypothermia was implemented in daily clinical practice. Adult patients who remained in a coma 24 h after CPR were included. Exclusion criteria were confirmed brain death after 24 h, concomitant traumatic brain injury, life expectancy of no more than several months caused by pre-existent disease, and absence of informed consent from a legal representative.

Neurological examination

Neurological examination, consisting of Glasgow Coma Score (GCS; only motor and eye score) and brain stem reflexes (pupillary light responses and corneal reflexes) was performed in every patient 24, 48, and 72 h after CPR. For current analyses, eye and motor scores were dichotomized; E1 (no eye opening) versus E2–4 (eye opening to pain-spontaneous eye opening) and M1–3 (no motor response-abnormal flexion to pain) versus M4–6 (withdrawal to pain-obey commands). Pupillary light responses and corneal reflexes were defined as present if at least a unilateral response was present. Our hypothesis was that an eye score of E1, a motor score of M1–3, bilaterally absent corneal reflexes, or bilaterally absent pupillary light responses would all predict an absent SEP; and that an eye score of E2–4, a motor score of M4–6, present corneal reflexes, or present pupillary light responses would all predict a present SEP. Complete neurological examination consisted of eye score, motor score, pupillary light responses and corneal reflexes. Our hypothesis was that the *combination* of an eye score of E1, a motor score of M1–3, bilaterally absent corneal reflexes, and bilaterally absent pupillary light responses would accurately predict an absent SEP; and that an eye score of E2–4, in combination with a motor score of M4–6, present corneal reflexes, and present pupillary light responses would accurately predict a present SEP.

Somatosensory evoked potentials

SEPs were recorded with standard procedures and were performed 24, 48, and 72 h after CPR [9]. Local clinical neurophysiologists in each contributing hospital assessed the recordings. The results for the cortical N20 response were documented as absent, present, or technically undeterminable. The median nerve SEP was defined as absent if the cortical N20 response was absent on both sides after left- and right-side median nerve stimulation, in the presence of a cervical potential. For logistical reasons, SEP was not always possible on weekends; if the 72-h SEP was due on a weekend day, the recording was postponed to Monday. SEPs with an undeterminable result were excluded from analysis. The results of 24- and 48-h SEPs were not available for treating physicians in order to avoid any influence of the test results on treatment decisions. The results of the 72-h SEP were disclosed to the treating physicians and if the SEP was absent, treatment was usually withdrawn.

Statistical analysis

Patient characteristics were summarized using descriptive statistics. Variables were expressed as mean and standard deviation, or when not normally distributed, as medians and inter-quartile ranges. The positive predictive values (PPV) for absent and present SEPs were calculated to indicate the proportion of the patients who have an SEP result as expected based on the neurological examination. We performed multivariable logistic regression analysis to relate the probability of an absent or present SEP to neurological examination (eye score, motor score, pupillary light responses, and corneal reflexes). Furthermore, the diagnostic accuracy (calculated as an area under the curve of a receiver operating characteristic curve) of neurological examination to predict an absent or present SEP was calculated.

Statistical uncertainty was expressed by the 95% confidence limits when appropriate, with statistical significance defined as $p \leq 0.05$. Analyses were performed by SPSS version 18.0 (SPSS Inc. IBM). Differences between areas under the curve (AUC) were analyzed with STATA version 10.

Results

Data of 407 patients were included, 67% were male and mean age was 63 years. The overall mortality was 89.7% (Table 1). A total of 781 SEPs were performed in this group, 401 were present and 299 absent. The remaining 81 were technically undeterminable and were excluded from

Table 1 Baseline characteristics

Patients included, <i>n</i>	407	
Male % (<i>n</i>)	67	(273)
Age, mean (SD)	63	(14)
APACHE II score, mean (SD)	25.5	(8.8)
Survival in days, median (IQR)	5	(3–11)
Overall mortality, % (<i>n</i>)	89.7	(365)
Mortality within 1 day, % (<i>n</i>)	4.7	(19)
Mortality within 2 days, % (<i>n</i>)	7.9	(32)
Mortality within 3 days, % (<i>n</i>)	17.2	(70)
SEP after 24 h	97 absent	134 present
SEP after 48 h	88 absent	128 present
SEP after 72 h	114 absent	139 present

SEP median nerve somatosensory evoked potentials, SD standard deviation, IQR inter-quartile range

further analysis. At 24, 48, and 72 h after CPR, respectively, 231, 216 and 253 SEPs were included.

In patients with a withdrawal response to painful stimuli (M4), we found an absent SEP in 19–31% at the different time points (Table 2). One patient localized painful stimuli at 48 h after CPR, but had an absent SEP. In patients with no motor response or extension to pain at 72 h after CPR, still 46% had a present SEP. Of the 60 patients with spontaneous eye opening, 22 had at least at once at the same moment an absent SEP.

Absent pupillary light responses after 72 h were the best predictor of an absent SEP (PPV 0.91 (0.79–0.96)) (Table 3). Motor score (M4–M6) after 48 and 72 h had the highest PPV for a present SEP (0.83 (0.68–0.91) and 0.83 (0.69–0.91)). All patients with M6 had present SEPs.

Due to low PPVs, i.e., close to 0.50, the eye score, motor score and pupillary light responses failed to discriminate SEP results in patients 24 h after CPR; only corneal reflexes were discriminative at 24 h for SEP results. Complete neurological examination at 48 (0.78 (0.72–0.85)) and 72 h (0.78 (0.72–0.84)) had the best

diagnostic accuracy for an absent, as well as a present SEP, but this values are only considered as “fair” (Table 4).

Discussion

This study has shown that in patients with postanoxic coma, absent or present cortical N20 responses of median nerve SEP cannot be predicted reliably by neurological examination. Absent pupillary light responses after 72 h were the best predictors of an absent SEP and a motor score of withdrawal to pain or better after 48 and 72 h was the best predictor of a present SEP. Complete neurological examination at 48 and 72 h achieved the best diagnostic accuracy for an absent, as well as a present SEP, but this accuracy could only be considered as “fair”. Therefore, when the clinical examination leaves doubt about the prognosis, the SEP has additional value. However, we should also realize that about half of the patients with a present SEP will still have a poor neurological outcome.

There is only one previous study on this subject [10]. In this study, results of the neurological examination and the EEG in 66 patients after cardiac arrest were retrospectively analyzed for their power to predict an absent SEP at day 3. Univariate analysis showed that absent pupillary light responses, absent corneal reflexes, myoclonus, or extensor or absent motor response to pain at day 1 (odds ratio (OR) 5.4–22.5) and day 3 (OR 7.9–22.6); and a malignant EEG at day 3 (OR 6.6) were all significantly associated with an absent SEP after 72 h. After multivariate analysis, absent corneal reflexes, extensor or absent motor response to pain or myoclonus at day 1 (OR 2.7–20.2) and day 3 (OR 4.1–17.3) and absent pupillary light responses or malignant EEG at day 3 (OR 3.1–7.8) remained predictors for an absent SEP. At day 1, the combination of myoclonus, extensor, or absent motor response to pain and absent corneal reflexes had a diagnostic accuracy of 0.89. At day 3, the same three predictors, together with absent pupillary

Table 2 Absent and present SEPs related to motor scores at three time intervals after CPR

Motor score	24 h after CPR			48 h after CPR			72 h after CPR		
	Number of patients	Absent SEP <i>n</i> (%)	Present SEP <i>n</i> (%)	Number of patients	Absent SEP <i>n</i> (%)	Present SEP <i>n</i> (%)	Number of patients	Absent SEP <i>n</i> (%)	Present SEP <i>n</i> (%)
1	141	65 (46)	76 (54)	133	63 (47)	70 (53)	132	71 (54)	61 (46)
2	20	14 (70)	6 (30)	16	9 (56)	7 (44)	34	19 (56)	15 (44)
3	31	7 (23)	24 (77)	23	8 (35)	15 (65)	31	11 (35)	20 (65)
4	35	11 (31)	24 (69)	31	6 (19)	25 (81)	39	8 (21)	31 (79)
5	3	0 (0)	3 (100)	8	1 (13)	7 (87)	3	0 (0)	3 (100)
6	0	0 (0)	0 (0)	1	0 (0)	1 (100)	4	0 (0)	4 (100)

CPR cardiopulmonary resuscitation, SEP median nerve somatosensory evoked potentials

Table 3 Positive predictive values for predicting an absent or present SEP in patients after CPR

	Positive predictive value for an absent SEP	Positive predictive value for a present SEP
Motor score 24 h	0.45 (0.38–0.52)	0.71 (0.55–0.83)
Motor score 48 h	0.47 (0.39–0.54)	0.83 (0.68–0.91)
Motor score 72 h	0.51 (0.44–0.58)	0.83 (0.69–0.91)
Eye score 24 h	0.44 (0.37–0.52)	0.67 (0.53–0.80)
Eye score 48 h	0.44 (0.36–0.52)	0.65 (0.53–0.76)
Eye score 72 h	0.54 (0.46–0.61)	0.75 (0.65–0.84)
Pupillary light responses 24 h	0.63 (0.47–0.77)	0.62 (0.55–0.69)
Pupillary light responses 48 h	0.86 (0.71–0.94)	0.69 (0.61–0.75)
Pupillary light responses 72 h	0.91 (0.79–0.96)	0.65 (0.58–0.71)
Corneal reflexes 24 h	0.63 (0.51–0.73)	0.67 (0.59–0.74)
Corneal reflexes 48 h	0.74 (0.61–0.84)	0.72 (0.64–0.79)
Corneal reflexes 72 h	0.77 (0.65–0.86)	0.67 (0.59–0.73)

All values are expressed with their 95% confidence limits. Positive predictive value for an absent or a present SEP = the proportion of the patients who have a SEP result as expected based on the neurological examination (eye score 1, motor score 1–3, bilaterally absent pupillary light responses or corneal reflexes for an absent SEP; eye score 2–4, motor score 4–6, present pupillary light responses or corneal reflexes for a present SEP)

SEP median nerve somatosensory evoked potentials, CPR cardiopulmonary resuscitation

Table 4 Diagnostic accuracy (as AUC) of neurological examination in predicting SEP results at 24, 48, and 72 h after CPR

	AUC	<i>p</i> value
Absent SEP 24 h	0.67 (0.60–0.74)	<0.001
Absent SEP 48 h	0.78 (0.72–0.85)	<0.001
Absent SEP 72 h	0.78 (0.72–0.84)	<0.001
Present SEP 24 h	0.67 (0.60–0.74)	<0.001
Present SEP 48 h	0.78 (0.72–0.85)	<0.001
Present SEP 72 h	0.78 (0.72–0.84)	<0.001

All values are expressed with their 95% confidence limits. The probability of an eye score of E1, a motor score of M1–3, bilaterally absent corneal reflexes, and bilaterally absent pupillary light responses reflexes for an absent SEP; the probability of an eye score of E2–4, a motor score of M4–6, present corneal reflexes and pupillary light responses for a present SEP

AUC area under the curve, SEP median nerve somatosensory evoked potentials, CPR cardiopulmonary resuscitation

light responses and a malignant EEG, had a diagnostic accuracy of 0.92.

The presence of spontaneous eye opening, but no tracking or blinking to commands, might reflect only subcortical activity (arousal) and does not necessarily

imply the impending development of awareness. Therefore, it is assumed to be an unreliable prognosticator [11–13]. This finding was confirmed in our study, as 37% of the patients with spontaneous eye opening had at least once at the same moment an absent SEP.

In our study, one patient who localized painful stimuli (M5) had an absent SEP 48 h after CPR. This was not expected, as localizing painful stimuli implies intact motor and sensory pathways [13]. The cortical N20 response is considered to be an activation of the primary somatosensory cortex following input from the thalamus. Delay or loss of the N20 peak implies an interruption of the connecting pathways between the cervicomedullary junction and the sensory cortex. Therefore, caution in interpreting SEPs should be taken in patients with focal brain lesions [12]. A possible explanation of our observation might be an overrating of the motor score. Previous studies have shown an excellent agreement for the inter-observer reliability of GCS (kappa 0.82–0.85), but only a “good” inter-observer agreement (kappa 0.63–0.77) for motor score alone [14, 15]. The highest degree of inter-observer agreement (0.86) for the motor score was obtained by neurology residents [14]. In our study, the neurological examination was also performed by other physicians than neurologists, which may have had a negative influence on the reliability of the results.

Other important considerations regarding interpretation of the SEP results are the reproducibility of SEP results in anoxic/non-traumatic coma and the reliability of SEP during and after hypothermia treatment. Previous studies mentioned good reproducibility of the SEP results, tested by repeated measurements [5, 16, 17]. Inter-observer disagreement was related to noise level and failure to strictly adhere to the guidelines. Reduction of noise level below 0.25 μ V during recordings improved the mean kappa from 0.34 (fair) to 0.74 (substantial) [9, 18]. SEP recorded during hypothermia seems to be a reliable predictor of poor outcome [19, 20]. Also, after treatment with hypothermia, SEP remains a reliable predictor, but some discussion arose after the publication of Leithner et al., who described one patient with an initial absent SEP after hypothermia treatment and good neurological outcome [7, 21–24].

Patient characteristics of the population of our study might have influenced the results. The PROPAC study included patients who were in coma 24 h after CPR without the administration of any sedative drugs. This selection explains the high mortality, and it might also explain the high proportion of patients with absent SEPs, which makes our results more confident.

A limitation of this study might be that the PROPAC study was performed before treatment with therapeutic hypothermia was routinely used. This may limit the usefulness of the results found in current clinical practice, as neurological examination is hampered by sedative medication

administered during hypothermia [7, 23, 25]. However, in daily clinical practice, neurological examination will be performed after wearing off of sedative drugs and before requesting a SEP. Furthermore, sedative drugs such as propofol or midazolam only seem to cause marginal effects on latency and amplitude of the cortical N20 responses [26–28].

Acknowledgments The PROPAC study was financially supported by a research grant from The Netherlands Heart Foundation and The Netherlands Brain Foundation. The funders had no role in the study design, the collection, analysis, and interpretation of data, the writing of the article, or the decision to submit it for publication.

Conflict of interest The authors declare that they have no conflicts of interest.

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References

- Levy DE, Caronna JJ, Singer BH, Lapinski RH, Frydman H, Plum F (1985) Predicting outcome from hypoxic-ischemic coma. *JAMA* 253:1420–1426
- Rothstein TL, Thomas EM, Sumi SM (1991) Predicting outcome in hypoxic-ischemic coma: a prospective clinical and electrophysiologic study. *Electroencephalogr Clin Neurophysiol* 79: 101–107
- Madl C, Kramer L, Domanovits H, Woolard RH, Gervais H, Gendo A, Eisenhuber E, Grimm G, Sterz F (2000) Improved outcome prediction in unconscious cardiac arrest survivors with sensory evoked potentials compared with clinical assessment. *Crit Care Med* 28:721–726
- Sherman AL, Tirschwell DL, Micklesen PJ, Longstreth WT Jr, Robinson LR (2000) Somatosensory potentials, CSF creatine kinase BB activity, and awakening after cardiac arrest. *Neurology* 54:889–894
- Zandbergen EG, Hijdra A, Koelman JH, Hart AA, Vos PE, Verbeek MM, de Haan RJ (2006) Prediction of poor outcome within the first 3 days of postanoxic coma. *Neurology* 66:62–68
- Prohl J, Rother J, Kluge S, de HG, Liepert J, Bodenburs S, Pawlik K, Kreymann G (2007) Prediction of short-term and long-term outcomes after cardiac arrest: a prospective multivariate approach combining biochemical, clinical, electrophysiological, and neuropsychological investigations. *Crit Care Med* 35:1230–1237
- Rossetti AO, Oddo M, Logroscino G, Kaplan PW (2010) Prognostication after cardiac arrest and hypothermia: a prospective study. *Ann Neurol* 67:301–307
- Wijdicks EF, Hijdra A, Young GB, Bassetti CL, Wiebe S (2006) Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 67:203–210
- Zandbergen EG, Hijdra A, de Haan RJ, van Dijk JG, Ongerboer de Visser BW, Spaans F, Tavy DL, Koelman JH (2006) Interobserver variation in the interpretation of SSEPs in anoxic-ischaemic coma. *Clin Neurophysiol* 117:1529–1535
- Daubin C, Guillotin D, Etard O, Gaillard C, du CD, Ramakers M, Bouchet B, Parienti JJ, Charbonneau P (2008) A clinical and EEG scoring system that predicts early cortical response (N20) to somatosensory evoked potentials and outcome after cardiac arrest. *BMC Cardiovasc Disord* 8:35
- Edgren E, Hedstrand U, Nordin M, Rydin E, Ronquist G (1987) Prediction of outcome after cardiac arrest. *Crit Care Med* 15:820–825
- Rothstein TL (2009) The utility of median somatosensory evoked potentials in anoxic-ischemic coma. *Rev Neurosci* 20:221–233
- Posner JB, SCSNPF (2007) Plum and Posner's diagnosis of stupor and coma, 4th edn. Oxford University Press, New York
- Wijdicks EF, Bamlet WR, Maramattom BV, Manno EM, McClelland RL (2005) Validation of a new coma scale: the FOUR score. *Ann Neurol* 58:585–593
- Stead LG, Wijdicks EF, Bhagra A, Kashyap R, Bellolio MF, Nash DL, Enduri S, Scheers R, William B (2009) Validation of a new coma scale, the FOUR score, in the emergency department. *Neurocrit Care* 10:50–54
- Madl C, Grimm G, Kramer L, Yeganehfar W, Sterz F, Schneider B, Kranz A, Schneeweiss B, Lenz K (1993) Early prediction of individual outcome after cardiopulmonary resuscitation. *Lancet* 341:855–858
- Madl C, Kramer L, Yeganehfar W, Eisenhuber E, Kranz A, Ratheiser K, Zauner C, Schneider B, Grimm G (1996) Detection of nontraumatic comatose patients with no benefit of intensive care treatment by recording of sensory evoked potentials. *Arch Neurol* 53:512–516
- Landis JR, Koch GG (1977) The measurement of observer agreement for categorical data. *Biometrics* 33:159–174
- Bouwes A, Binnekade JM, Zandstra DF, Koelman JH, van Schaik IN, Hijdra A, Horn J (2009) Somatosensory evoked potentials during mild hypothermia after cardiopulmonary resuscitation. *Neurology* 73:1457–1461
- Tiainen M, Kovala TT, Takkunen OS, Roine RO (2005) Somatosensory and brainstem auditory evoked potentials in cardiac arrest patients treated with hypothermia. *Crit Care Med* 33:1736–1740
- Fugate JE, Wijdicks EF, Mandrekar J, Claassen DO, Manno EM, White RD, Bell MR, Rabinstein AA (2010) Predictors of neurologic outcome in hypothermia after cardiac arrest. *Ann Neurol* 68:907–914
- Leithner C, Ploner CJ, Hasper D, Storm C (2010) Does hypothermia influence the predictive value of bilateral absent N20 after cardiac arrest? *Neurology* 74:965–969
- Samaniego EA, Mlynash M, Caulfield AF, Eyngorn I, Wijman CA (2011) Sedation confounds outcome prediction in cardiac arrest survivors treated with hypothermia. *Neurocrit Care* 15:113–119
- Bouwes A, Binnekade JM, Kuiper MA, Bosch FH, Zandstra DF, Toornvliet AC, Moeniralam HS, Kors BM, Koelman JH, Verbeek MM, Weinstein HC, Hijdra A, Horn J (2010) Prognosis and prognostication after cardiac arrest and hypothermia; results of PROPACII, a Dutch multicenter, prospective cohort study. *Intensive Care Med* 36:S297
- Al Thenayan E, Savard M, Sharpe M, Norton L, Young B (2008) Predictors of poor neurologic outcome after induced mild hypothermia following cardiac arrest. *Neurology* 71:1535–1537
- Koht A, Schutz W, Schmidt G, Schramm J, Watanabe E (1988) Effects of etomidate, midazolam, and thiopental on median nerve somatosensory evoked potentials and the additive effects of fentanyl and nitrous oxide. *Anesth Analg* 67:435–441
- Scheepstra GL, de Lange JJ, Booij LH, Ros HH (1989) Median nerve evoked potentials during propofol anaesthesia. *Br J Anaesth* 62:92–94
- Sloan TB, Fugina ML, Toleikis JR (1990) Effects of midazolam on median nerve somatosensory evoked potentials. *Br J Anaesth* 64:590–593